REMARKS/ARGUMENTS

Claims 1-3 and 5-26 were pending in the application. Claims 21-26 were withdrawn from consideration. Accordingly, claims 1-3 and 5-20 are currently under consideration. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented.

Reconsideration is respectfully requested in view of the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

A. Rejections Under 35 U.S.C. § 103(a)

Claims 1-3 and 5-20 remain rejected under 35 U.S.C. §103(a) as being unpatentable over JP3109328 in view of Elson (*Current Topics in Microbiology*, 146:29-33, 1989).

Applicants respectfully traverse the grounds for rejection and further submit, in support of their position, Declarations under 37 C.F.R. §1.132 of Dr. Jan Holmgren and Dr. Cecil Czerkinsky, who are experts in the field of mucosal immunology and oral/mucosal tolerance.

(i) The Examiner states that the Specification does not teach "specific" tolerance induction since it does not demonstrate that CTB does not affect other control antigens not administered at the same time or via the same route of administration. Applicants respectfully traverse.

The Specification shows that mucosal administration of CTB (Example 5, pages 44-46; group 4) has no effect (Tables 6 and 7, groups 4 and 6) on T-cell response to tetanus toxin immunization. Only when tetanus toxin is given together via mucosal administration is a tolerizing effect seen (Tables 6 and 7 groups 1 and 6). Furthermore, the data in the specification (Tables 2 and 3, group 7) also shows that CTB has no effect on immune responses to other antigens if they are not administered together via the mucosal route since the autoimmune response to the islet antigen causing diabetes is not effected at all. (Mice receiving 1000 μg CTB develop diabetes at the same

rate as the sham-fed animals; Tables 2 and 3, groups 7 and 9). These data conclusively demonstrate that CTB alone given via an mucosal route has no general tolerogenic effect, but is highly antigen specific and dependent on "administering to a mucosal surface of the individual a composition comprising an effective amount of a mucosal binding component selected from the group consisting of a cholera toxin B peptide (CTB) ... in an unconjugated form" as specified in independent claims 1, 12 and 20.

(ii) The Examiner contends that JP3109328, by administering CTB and antigen (cells) in an unconjugated form meets the scope of the instant claims (which do not require simultaneous administration). The Examiner further contends that Elson shows that it is very important for CTB to be administered by the same route and the same time as the antigen and that CTB administered orally does not stimulate antibody response to the antigen. Thus, the Examiner believes that it would have been obvious to administer CTB and antigen by oral route to induce tolerance. Applicants respectfully traverse.

JP3109328 teaches administration of CTB on or before the administration of the antigen in order to generally suppress the immune system from rejecting the graft. Administration is preferably through non-transintestinal (mucosal) routes such as the vein, peritoneal cavity or muscle. It might well be that administering CTB by a non-mucosal route will generate general immunosuppression as taught in JP3109328,

However, the Specification in Example 1 (pages 37-40; Tables 2 and 3, groups 7 and 9) shows that CTB when administered by itself via the mucosal route does not cause any general immunosuppression (inhibition of diabetes in the NOD mouse). A recent publication by Bregenholt *et al.* (Scand. J. Immunol., 57(5):432 (2003)) (Attachment 1) confirms (*see* Figure 3C) that CTB when administered by itself via the mucosal route does not cause any general immunosuppression. It is evident that in a very large dose range -- 1000 μg (Specification) to 1 μg (Bregenholt *et al.*, Fig. 3C) -- no general immunosuppression is observed when CTB is administered by itself. Further corroboration of this result was shown by Bergerot *et al.* (Proc. Natl. Acad. Sci (USA) 94:4610-4614 (1997)) (Attachment 2) who demonstrated that orally-administered CTB alone has no effect on suppression of the autoimmune response causing diabetes, (Bergerot *et al.*, Fig. 1). Therefore it is

evident that CTB does not work as a general immunosuppressant when administered alone via the mucosal route.

In his Declaration under 37 C.F.R. §1.132 Dr. Jan Holmgren states that JP3109328 "teaches that pretreatment with CTB can be used, *preferably by a non-mucosal route*, to facilitate better survival of transplanted tissue but any such effect has nothing to do with the mucosal induction of peripheral-systemic tolerance ... but is rather an unspecific killing effect of high doses of CTB on lymphocytes, where it has been described that the main effector cells for graft rejections, CD8+ CTLs, are especially sensitive to this unspecific cytotoxic action of high doses of CTB."

Likewise, in his Declaration under 37 C.F.R. §1.132, Dr. Cecil Czerkinsky states that "non specific tolerance has been documented for cholera toxin and anticipated for cholera toxin B subunit given by a non mucosal, i.e., a systemic (intraveinous, intramuscular) route ... because these molecules have been shown to be directly toxic on certain lymphocyte subsets (CD8+ cytotoxic T cells) which are known to play a critical role in graft rejection."

Both experts agree that this nonspecific cytotoxic action of high doses of CTB administered by a non-mucosal route does not relate to "inducing specific sustained immunological tolerance in an individual to a target antigen, comprising administering to a mucosal surface of the individual a composition comprising an effective combination of an inducing agent and a mucosal binding component selected from the group consisting of a cholera toxin B peptide (CTB) ..." as specified in independent claim 1.

(iii) Elson refers to lack of stimulation of antibody responses by mucosal administration of antigen and CTB primarily based on two references in his review (*see* page 31 first paragraph). One reference (Mckenzie and Halsey 1984 J Immunol 133:1818-1824) (Attachment 3) demonstrates the following: when an antigen, horseradish peroxidase (HRP), is administered alone to a mucosal surface it stimulates both mucosal and serum antibodies to HRP (*see* Mckenzie and Halsey, Tables I and II). However, by co-administering CTB and HRP, there is absolutely no effect (antibody response to HRP does not change either up or down) unless the CTB and HRP are administered in conjugated form. Therefore, from these experiments, the only conclusion that can be drawn is that

CTB co-administered with antigen in a non-conjugated form has no effect whatsoever either as an adjuvant or tolerogen. While Elson states that "CTB does not induce antibodies" the papers which Elson refers to show that unconjugated CTB has no effect, it neither enhances nor suppresses them. In order for CTB to have an effect as an adjuvant it needs to be chemical conjugated to HRP (*see* Mckenzie and Halsey, Tables I and II). The other article referred to by Elson is authored by Lycke and Holmgren. An expert declaration by Dr. Holmgren, a co-author og that paper accompanies this response. In his expert declaration, Dr. Holmgren states "that mucosally administered CTB can induce such tolerance ***only when conjugated with*** selected antigens, which further supports the notion that the claimed invention by Dr. Petersen is both novel and unexpected." (emphasis original)

Elson merely demonstrates that it is possible to stimulate ("adjuvant" effect) an immune response to antigens co-administered with CTB in conjugated form via the mucosal route which has been known for a long time. (see expert declarations of Drs. Holmgren and Czerkinsky). Further, since the papers referred to by Elson were trying to induce an antibody response to the antigen (KLH) by co-administering with CTB (examining only the adjuvant effect) it teaches away from the present invention.

In his expert declaration, Dr. Holmgren states that Elson (and others before him) have taught that "cholera toxin B subunit (CTB) is by itself a strong mucosal immunogen and may also serve as an adjuvant for admixed, mucosally co-administered antigens in ***stimulating*** mucosal and peripheral-systemic immune responses." The art does not teach that mucosally administered CTB could instead, or alternatively, induce peripheral-systemic tolerance for selected co-administered admixed antigens as taught by the present application.

Further, as stated in his declaration by Dr. Czerkinsky, immunological tolerance induced by mucosal co-administration of CTB and an antigen was previously (and obviously erroneously) suggested to require physical association of both compounds to be effective by Sun *et al.* (Proc. Natl. Acad. Sci (USA) 91:10795-99 (1994)) (Attachment 4) (*see also,* "mucosally administered CTB can induce such tolerance only when conjugated with selected antigens ..." (emphasis added); declaration of Dr. Holmgren). This further supports the position that the claimed invention of administering "a composition comprising an effective combination of an inducing agent and a

mucosal binding component selected from the group consisting of a cholera toxin B peptide (CTB) ... in an unconjugated form" is both novel and unexpected. (emphasis added)

(iv) JP3109328 teaches that administration of CTB induces general immunosuppression to antigens when administered via a non-mucosal route. The present specification and the enclosed references clearly demonstrate that CTB does not induce general immunosuppression when administered via an mucosal route. Elson only demonstrates that CTB can enhance an antibody response to an antigen when co-administered in a conjugated form. Neither Elson nor JP3109328 teach, mention or suggest any tolerance induction using CTB co-administered with antigen in an unconjugated form.

Experts in the field (Drs. Holmgren and Czerkinsky) find that JP3109328 and Elson in combination or by themselves do not teach one skilled in the art the claimed invention of tolerance induction by mucosal co-administration of CTB and antigen. The pre-existing art taught away from the claimed invention by failing to show that administering unconjugated CTB with an antigen had any effect on immune response to the antigen. Drs. Holmgren and Czerkinsky agree that the claimed invention is unpredictable from the teachings of Elson and Tsuru (JP3109328) and unexpected in view of the pre-existing art.

Applicants submit that JP3109328 and Elson together do not teach all the elements of the pending claims (in particular, specific tolerance induction by mucosal co-administration with CTB). Further, in view of the prior state of the art the claimed invention is novel and unexpected (in particular, the tolerogenic effect of co-administration in unconjugated form). Further, experts in the field have stated in their sworn declarations that the claimed invention is unexpected and not predictable from the Elson and JP3109328 references and the state of the art. Therefore, Applicants respectfully request that the rejection under 35 USC § 103 be withdrawn.

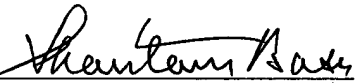
CONCLUSION

In light of the arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant(s) petition(s) for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. (273802002200).

Dated: July 14, 2003

Respectfully submitted,

By 

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